Development of Risk Simulation Software for Outcome Prediction and Economic Assessment of Diabetes Mellitus

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Abstract
We referred to epidemiological data from Japan and abroad related to the development and progression of diabetic retinopathy, diabetic nephropathy, an diabetic neuropathy, ischemic heart disease, and cerebrovascular disease to design risk simulation software that, when patient background data and test results are entered, graphs the incidence rates of complications and lifetime medical costs and enables calculation of expected life years and quality-adjusted life years (QALYs). We constructed 6 submodels related to retinopathy, nephropathy, and neuropathy transitions and to coronary heart disease, stroke, and mortality based on epidemiological studies from Japan and abroad. Based on statistical data, including “National Healthcare Expenditures” and “Patient Surveys”, and receipt surveys in healthcare institutions, we estimated the annual treatment costs that arise in each stage of the complications. In addition, we used a literature reference from abroad to set utility values in each stage of the complications in order to calculate QALYs. To validate our software for the progression of retinopathy we used the clinical data provided from 2 hospitals and we assessed how closely the retinopathy and nephropathy stage distribution 10 yr later predicted by our software and the actual disease stages matched. Although small discrepancies were seen from the absolute values, the results of the estimations related to the progression of retinopathy and nephropathy showed that the trends were very similar, and the estimates generally appeared to be valid. Our software makes it possible to perceive the effect on future health status and treatment costs visually by inputting the various test values before and after the intervention, and it seemed to be highly useful for evaluating medical support, patient education, and preventive measures, and for designing health policy.

Key words: diabetes mellitus, retinopathy, nephropathy, neuropathy, ischemic heart disease, cerebrovascular disease, simulation software, quality adjusted life years, economic evaluation

Introduction
Diabetes mellitus pursues a long course and gives rise to a variety of complications, including ischemic heart disease (angina pectoris, myocardial infarction) and cerebrovascular disease (cerebral infarction, cerebral hemorrhage) in addition to microangiopathy as typified by nephropathy, retinopathy, and neuropathy. The number of diabetic nephropathy patients has been steadily increasing in recent years, and since becoming the leading underlying disease responsible for the institution of dialysis therapy in 1999, approximately 12,000 patients have been started on dialysis annually. Most of them have type 2 diabetes (non-insulin-dependent diabetes), and the importance of early detection and appropriate treatment has been pointed out. However, it is difficult to determine the effect of such interventions on patients’ long-term outcome or
lifetime healthcare costs by means of prospective studies.

Simulations based on epidemiologic data, etc., have been attempted in Western countries. For example, based on the results of the Diabetes Control and Complications Trial (DCCT), the DCCT Research Group conducted a comparative study in which they used a simulation model to estimate the differences in long-term outcome and lifetime medical costs between a conventional insulin therapy group and an intensive insulin therapy group of type 1 diabetes patients. In addition, the United States Centers for Disease Control (CDC) Diabetes Cost-effectiveness Group estimated the cost-effectiveness of using intensive glycemic control, intensified hypertension control, and tight lipid control to treat type 1 diabetes patients by using a simulation model created on the basis of the results of the United Kingdom Prospective Diabetes Study (UKPDS), which was conducted in the United Kingdom.

However, since clinical trial data and epidemiologic data obtained in Western countries were used in those studies, the outcome prediction results obtained by using their simulation models cannot very well simply be applied to Japan unmodified. Moreover, because they are the results of calculations made using healthcare unit costs in other countries, they can hardly ever be used for reference when estimating treatment costs in Japan, where the healthcare reimbursement system is different.

We referred to epidemiological data from Japan and abroad related to the development and progression of diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, ischemic heart disease, and cerebrovascular disease to design risk simulation software that, when patient background data and test results are entered, graphs the incidence rates of complications and lifetime medical costs and enables calculation of expected life years and quality-adjusted life years (QALYs). In this article we summarize the software and report the results of validating it.

❖ Methods

1. Computation logic

The data from the Kumamoto Study in Japan were used as the basic epidemiological data, and using the UKPDS in the United Kingdom, the Framingham Heart Study in the United States, etc., for reference we constructed 6 submodels related to retinopathy, nephropathy, and neuropathy transitions and to coronary heart disease (CHD), stroke, and mortality.

1.1. Retinopathy submodel

A Markov model composed of 5 stages, “no retinopathy”, “simple diabetic retinopathy (SDR)”, “pre-proliferative diabetic retinopathy (prePDR)”, “proliferative diabetic retinopathy (PDR)”, and “blindness”, was used as the submodel of retinopathy (Figure 1). Transitions between these stages toward higher stages of severity occur at fixed annual rates. No reversals were set. The data from the conventional insulin injection therapy (CIT) group in the Kumamoto Study were used as the basis of the annual transition probabilities. However, because no transition probability for “PDR → blindness” was reported in the Kumamoto Study, we used the value reported by Moss et al. in the United States.

Based on the data from the multiple insulin injection therapy (MIT) group in the Kumamoto Study, transition probabilities for the intervals from “no retinopathy” to “PDR” were used as the subjects of risk adjustment according to HbA1c values. More specifically, the more the HbA1c values improved, the later the progression of retinopathy was set for the intervals “no retinopathy → SDR”, “SDR → prePDR”, and
The actual risk adjustment method was as follows:

$$RR_i = RR_t \times \left( \frac{\ln(v_i/v_c)}{\ln(v_t/v_c)} \right),$$

where

- $RR_i$: adjustment coefficient of the $i$-th patient simulated
- $RR_t$: relative risk observed in the clinical study
- $v_i$: numerical value of the risk factor of the $i$-th patient
- $v_t$: mean value of the risk factor attained by the treated group in the clinical study ($=7.2$)
- $v_c$: mean value of the risk factor of the control group in the clinical study ($=9.4$)

Relative risk in the MIT group, with the CIT group in the Kumamoto Study serving as the standard, was used to set the relative risk ($RR_t$) values when HbA1c changed, as follows:

- No retinopathy $\rightarrow$ SDR: 0.27
- SDR $\rightarrow$ prePDR: 0.27
- prePDR $\rightarrow$ PDR: 0.75

For example, the adjustment of transition probability from “no retinopathy” to “SDR” when HbA1c = 8.0% would be:

$$RR_i = 0.27 \times \left( \frac{\ln(8.0/9.4)}{\ln(7.2/9.4)} \right) = 0.45$$

Therefore, multiplying by the basic value 9.3%, the transition probability would be:

$$9.3\% \times 0.45 = 4.2\%$$

The relation between HbA1c values and transition probabilities from “no retinopathy” to “SDR” is shown in Figure 2.

In addition, a risk adjustment according to systolic blood pressure (SBP) was made for the probability of the transition from SDR to prePDR, based on the UKPDS data.  

We used the relative risk of the intervention group, with the conventional treatment group (control group) in the UKPDS serving as the standard, to set the relative risk ($RR_t$) of SBP change, as follows:

- SDR $\rightarrow$ prePDR: 0.67

### 1.2. Nephropathy submodel

A Markov model composed of 5 stages, “no nephropathy (normoalbuminuria)”, “microalbuminuria (Micro)”, “macroalbuminuria (Macro)”, “renal failure in conservative phase”, and “hemodialysis”, was used as the submodel of nephropathy (Figure 3). The same as in the retinopathy model, transitions to more severe stages occur at fixed annual rates, and no reversals were set. The data for the CIT group in the Kumamoto Study were used as the basis for establishing the annual transition probabilities.

**Figure 2. Example of the relation between HbA1c values and transition probabilities from “no retinopathy” to “SDR”**

**Figure 3. Submodel of nephropathy: the data of the control group in the Kumamoto Study were used as the basis of the annual transition probabilities**
The intervals from “no nephropathy” to “macroalbuminuria” were the subjects of the risk adjustments according to HbA1c based on the data from the MIT group in the Kumamoto Study. In addition, risk adjustments according to SBP for the transition probabilities of the intervals from “no nephropathy” to “macroalbuminuria” were made based on the UKPDS data. The adjustment methods were the same as used for retinopathy.

Relative risk when HbA1c changes (RRt)
No nephropathy → Micro: 0.40
Micro → Macro : 0.32

Relative risk when SBP changes (RRt)
No nephropathy → Micro: 0.71
Micro → Macro : 0.63

1.3. Neuropathy submodel

The neuropathy submodel is composed of 5 stages, “no neuropathy”, “symptomatic neuropathy”, “lower extremity amputation (LEA) 1”, “LEA 2”, and “foot ulcer”. Since LEA is not limited to a single event, we included it in the model twice. Because no Japanese data related to transition probabilities for neuropathy exist, we used the transition probabilities according to the report by the CDC Diabetes Cost-Effectiveness Group and modified them by referring to the opinion of a medical expert (Figure 4).

1.4. Ischemic heart disease submodel

We used a risk computation formula based on the results of the analysis of the Framingham Study conducted in the United States to calculate the incidence rate of ischemic heart disease. There are several reports in the Framingham estimates, but we used the formula reported by Anderson et al. in our software.

Age, sex, total cholesterol, HDL cholesterol, SBP, whether a smoker, whether abnormal glucose tolerance present, and whether left ventricular hypertrophy present are the factors used to calculate risk in their formula.

The intermediate indicators, a, m, µ, σ, and u, were calculated, when the following values were used:
SMKG: smoker, 1; non-smoker, 0
LVH: left ventricular hypertrophy present, 1; absent, 0
DM: abnormal glucose tolerance present, 1; absent, 0.

Calculation of a,
\[ a = 11.1122 - 0.9119 \times \log(SBP) - 0.2767 \times SMKG - 0.7181 \times \log(TC/HDL) - 0.5865 \times LVH, \]

Calculation of m,
For males : \[ m = a - 1.4792 \times \log(age) - 0.1759 \times \text{DM} \]
For females : \[ m = a - 5.8549 + 1.8515 \times [\log(age/74)]^2 - 0.3758 \times \text{DM} \]

Calculation of µ,
\[ \mu = 4.4181 + m \]
Calculation of $\sigma$
$$\sigma = \exp(-0.3155 - 0.2784 \times m)$$

Calculation of $u$
$$u = \frac{\log(t) - \mu}{\sigma}$$

The probability of CHD by $t$ years later, $p$, was calculated by using the formula:
$$p = 1 - \exp(-\exp(u))$$

However, since the incidence rates of ischemic heart disease in the United States and Japan are known to differ considerably, we multiplied the above incidence rate by 0.23 based on the results of the Hisayama Study 6), an epidemiological survey conducted in Japan (Table 1).

### 1.5. Stroke submodel

The development of stroke was also estimated by a Framingham risk estimation formula, the same as for ischemic heart disease.

The intermediate indicators, $\mu$, $\sigma$, and $u$ were computed, when the following values were used:
- **SEX**: male, 0; female, 1
- **SMKG**: smoker, 1; non-smoker, 0
- **LVH**: left ventricular hypertrophy present, 1; absent, 0
- **DM**: abnormal glucose tolerance present, 1; absent, 0

$$\mu = 26.5116 + \text{SEX} \times 0.2019 - 2.3741 \times \log(\text{AGE}) - 2.4643 \times \log(\text{SBP}) - 0.3914 \times \text{SMKG} - 0.0229 \times \log(\text{TC} / \text{HDL}) - 0.3087 \times \text{DM} - 0.2627 \times \text{DM} \times \text{sex} - 0.2355 \times \text{LVH}$$

$\sigma = \text{calculation of } \exp(-0.4312)$

$$u = \frac{\log(t) - \mu}{\sigma}$$

The probability of the occurrence of stroke by $t$ years later, $p$, was calculated by using the formula:
$$p = 1 - \exp(-\exp(u))$$

In addition, since the incidence rates of stroke in the United States and Japan are known to differ considerably, we multiplied the above incidence rate by 2.16 based on the results of the Hisayama Study 6) (Table 1).

### 1.6. Mortality submodel

We used the mortality rates according to age and sex in the simple life tables reported annually by the Statistics and Information Department, Minister’s Secretariat, Ministry of Health, Labour and Welfare as the basic values, and estimated annual mortality rates by weighting each stage of nephropathy. However, we assumed that everyone had died by 100 years of age. We set the mortality rate at 1.5 times the natural mortality rate in the Macro stage, at 2 times the natural mortality rate in renal failure, and at a uniform 14.1%/yr during dialysis irrespective of the natural mortality rate 7).

However, we assumed that patients who had undergone leg amputation die at a fixed probability rate, and referring to the opinion of a medical expert, we set it at 5.0%/yr. We used 16.2%/yr as the probability of acute stage death of patients who developed
ischemic heart disease\textsuperscript{8}). In addition, we assumed that patients who experience a stroke die at fixed probability rates, and we classified them according to sex and age as shown in Table 2\textsuperscript{9}).

1.7. Other settings

Based on statistical data, including “National Healthcare Expenditures” and “Patient Surveys”, and receipt surveys in healthcare institutions, we estimated the annual treatment costs (FY 2000) that arise in each stage of the complications (Table 3). In addition, we used a literature reference from abroad\textsuperscript{10}) to set utility values (QOL weights, with complete health set equal to 1.00 and death set equal to 0.00) in each stage of the complications in order to calculate QALYs (Table 3).

2. Model Validation

To validate our software for the progression of retinopathy we input the clinical data of 260 patients who did not have retinopathy initially among the type 2 diabetes patients who were examined for the first time at the Diabetes Center of Tokyo Women’s Medical University during the period 1983–1985 and whom it was possible to follow up for 10 yr, and we assessed how closely the retinopathy stage distribution 10 yr later predicted by our software and the actual disease stages matched\textsuperscript{11}).

To validate our software for the progression of nephropathy we input the clinical data of 416 type 2 diabetes patients who were examined in the internal medicine department of Saiseikai Central Hospital and whom it was possible to follow up for 10 yr, and we assessed how closely the nephropathy stage distribution 10 yr later predicted by our software and the actual stages matched in an initially “no nephropathy (normoalbuminuria)” patient group and an initially “microalbuminuria” group\textsuperscript{12}).

3. Simulation case

As an example of simulation using our software, we attempted to calculate the effect on long-term outcome and treatment costs when diabetes disease management was performed for a “50-year-old male with a 5-year history of diabetes who was a non-smoker and did not have left ventricular hypertrophy, retinop-

<table>
<thead>
<tr>
<th>Status</th>
<th>Annual treatment costs (¥)</th>
<th>Utility values (QOL weights)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No retinopathy</td>
<td>2,240</td>
<td>1.00</td>
</tr>
<tr>
<td>Simple diabetic retinopathy (SDR)</td>
<td>2,240</td>
<td>0.52</td>
</tr>
<tr>
<td>Pre-proliferative diabetic retinopathy (prePDR)</td>
<td>27,339</td>
<td>0.52</td>
</tr>
<tr>
<td>Proliferative diabetic retinopathy (PDR)</td>
<td>72,041</td>
<td>0.52</td>
</tr>
<tr>
<td>Blindness</td>
<td>42,741</td>
<td>0.45</td>
</tr>
<tr>
<td>No nephropathy (normoalbuminuria)</td>
<td>74,340</td>
<td>1.00</td>
</tr>
<tr>
<td>Microalbuminuria (Micro)</td>
<td>76,070</td>
<td>0.53</td>
</tr>
<tr>
<td>Macroalbuminuria (Macro)</td>
<td>79,850</td>
<td>0.53</td>
</tr>
<tr>
<td>Renal failure in conservative phase</td>
<td>95,390</td>
<td>0.48</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>5,382,432</td>
<td>0.48</td>
</tr>
<tr>
<td>No neuropathy</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>58,034</td>
<td>0.52</td>
</tr>
<tr>
<td>Foot ulcer</td>
<td>621,258</td>
<td></td>
</tr>
<tr>
<td>Lower extremity amputation (LEA)</td>
<td>1,386,274</td>
<td>0.52</td>
</tr>
<tr>
<td>Myocardial infarction (first year)</td>
<td>1,088,520</td>
<td>0.54</td>
</tr>
<tr>
<td>Myocardial infarction (after second year)</td>
<td>279,600</td>
<td>1.00</td>
</tr>
<tr>
<td>Stroke (first year)</td>
<td>877,150</td>
<td>0.49</td>
</tr>
<tr>
<td>Stroke (after second year)</td>
<td>213,200</td>
<td>1.00</td>
</tr>
</tbody>
</table>
athy, nephropathy, or neuropathy”. Based on the results of “Study on disease management for the prevention of progression of diabetes” (principal investigator: Akira Takeda) from the Health Labour Sciences Research Grant, 2001[13], it was postulated that when diabetes disease management was not conducted the mean test data values “at the time of enrollment” were maintained over the patient’s lifetime, whereas when diabetes disease management was conducted, the mean test data values in the “36th month of intervention” were maintained over the patient’s lifetime (Table 4).

Table 4 Changes of mean test data by diabetes disease management (Ref. 13)

<table>
<thead>
<tr>
<th></th>
<th>At the time of enrollment</th>
<th>36th month of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>7.1%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Systolic blood pressure (SBP)</td>
<td>133.8</td>
<td>131.5</td>
</tr>
<tr>
<td>Total cholesterol (TC)</td>
<td>209.4</td>
<td>222.2</td>
</tr>
<tr>
<td>HDL cholesterol (HDL)</td>
<td>60.2</td>
<td>56.1</td>
</tr>
</tbody>
</table>

Figure 5. Result of the simulation about the lifetime incidence rates of complications (Left: Before disease management intervention, Right: After disease management intervention)

Figure 6. Result of the simulation about the lifetime health care cost (Left: Before disease management intervention, Right: After disease management intervention)

Results

1. Model validation

Although small discrepancies were seen from the absolute values, the results of the estimations related to the progression of retinopathy showed that the trends were very similar, and the estimates generally appeared to be valid.

The results of the estimates related to the progression of nephropathy showed a relatively close match between the patients’ data and simulation results in the cases from “normoalbuminuria” onward. However, in the cases from “microalbuminuria” onward, there was a large discrepancy between the results of the simulation and the actual distribution of nephropathy, and that appeared to have been attributable to the existence of cases that actually reverted from microalbuminuria to normal.

2. Simulation case

The results of the simulation predicted that, with the exception of ischemic heart disease, the lifetime incidence rates of complications would decrease (Figure 5). In particular, it was predicted that retinopathy and nephropathy would decrease approximately 60%.
The expected treatment cost required for the care of the complications decreased from ¥7,980,000 to ¥4,460,000. Examination of the data according to complication showed that the decrease in cost related to nephropathy was the most marked (Figure 6). That was because of the large decrease in the incidence rate of hemodialysis from 14.7% to 5.8%.

❖ Conclusion

Our software makes it possible to perceive the effect on future health status and treatment costs visually by inputting the various test values before and after the intervention, and it seemed to be highly useful for evaluating medical support, patient education, and preventive measures, and for designing health policy.

In the future we would like to collect additional clinical research data, epidemiological data, and cost data in Japan, and to refine the model.

❖ Acknowledgments

We wish to express our gratitude to Prof. Naoko Tajima of The Jikei University School of Medicine, Prof. Ryuzo Kawamori and Dr. Yasushi Tanaka of Juntendo University, Dr. Kenpei Matsuoka, Dr. Yoshihito Atsumi, Dr. Kazuhiro Hosokawa, and Dr. Atsuko Mokubo of Saiseikai Central Hospital, Prof. Yasuhiro Iwamoto and Dr. Tomoko Nakagami of Tokyo Women’s Medical University, Prof. Makoto Tominaga of Yamagata University, Dr. Mariko Ohishi of the Ohishi Naika Clinic, and Prof. Tatsuro Ishibashi of Kyushu University.

❖ References


